Anisotropic convergence of dendritic macromolecules facilitated by a heteroleptic metal-organic polyhedron scaffold

ChemComm

COMMUNICATION

Anisotropic convergence of dendritic macromolecules facilitated by a heteroleptic metal-organic polyhedron scaffold

Kenichiro Omoto,[a] Nobuhiko Hosono,[a]* Mika Gochomori,[a] Ken Albrecht,[b,c] Kimihisa Yamamoto[b,c] and Susumu Kitagawa[a]*

Anisotropic dendrimers with bipolar shapes were systematically obtained using a heteroleptic metal-organic polyhedron (MOP) as a robust core scaffold. The structure of one of these polyhedral shapes was unambiguously determined by single-crystal X-ray analysis, which revealed that the bulky dendrons converge to both polars position of the heteroleptic MOP core.

The high-precision synthesis of nanometer-sized giant macromolecules with well-defined shapes and chemical structures is a fundamental topic in chemistry.[1] From lessons learnt from nature, we have come to recognize that most biomacromolecules, including proteins, construct their own tertiary structures with anisotropic and asymmetric molecular arrangements, through the self-assembly of many different molecular/macromolecular components.[2] Such structurally anisotropic products subsequently regulate self-organizational processes that result in further asymmetric constructions within organisms, for example in the membranes and structures of cells, and are considered to be the essence of entire life systems. Self-assembly is a powerful tool that enables the facile construction of giant molecules; however, the structural anisotropies of self-assembled products are barely controllable in a rational way since entropic and steric contributions dominate in high-molecular-weight molecules, resulting in isotropic and spherical shapes at the end of the formation process.

Dendrimers are a class of branched macromolecule that typically have spherical shapes with isotropic cores.[3] Despite significant studies toward the construction of nanometer-sized

dendritic macromolecules using self-assembly principles, anisotropic dendrimer design has been limited and remains a formidable challenge.[3a,f,g] An essential issue that requires addressing is the lack of self-assembly scaffolds that afford robust cores that precisely control the three-dimensional arrangements of dendritic components in order to prevent and balance steric congestion.

Herein, we introduce a facile synthesis approach to dendritic macromolecules with bipolar anisotropic shapes through the use of a heteroleptic metal-organic polyhedron (MOP) core. A MOP is a type of discrete cage-like complex that possesses a spherical shape that is formed through the coordination-driven self-assembly of multiple ditopic bent ligands and metal ions.[4] As a common representative homoleptic cubocctahedral MOP, $Cu_{24}IpR_{24}$ is composed of 24 isophthalates (IpR^{2-}, where Ip and R denote isophthalate and the substituent, respectively) interconnected with 12 dicopper paddlewheel clusters, possessing the isotropic spherical shape with a diameter of ca. 2.4 nm (Fig. 1a).[5]

MOPs have recently been used as cage functionalities for host-guest chemistry and gas storage/separation materials,[4b,c] as well as core scaffolds for the facile syntheses of multi-armed macromolecules and polymer networks.[6] The vertices of each ligand can be functionalized with macromolecules, including synthetic polymers[6a,b,d,f] and bio-polymers,[6c] to afford a variety of complex architectures; however, only spherical products with isotropic ligand allocations can be formed. On the other hand, equimolar combinations of isophthalate and linker ligands, such as 3,3-(ethyne-1,2-diyl)dibenzoate (L^{2-}), have been reported to provide "heteroleptic" MOPs with bipolar ligand arrangements (Fig. 1b).[5b] Recently, we developed a new class of anisotropically shaped star polymers using this heteroleptic MOP architecture as the core.[7] We found that the star polymer on a heteroleptic MOP core is significantly more stable than that on a homoleptic MOP core, which indicates that steric factors may affect the self-assembly process.

In this study, we envisaged that such a heteroleptic bipolar scaffold would act as the robust core for anisotropic macromolecules; consequently we developed a novel approach

a. Institute for Integrated Cell-Material Sciences (WPI-iCeMS), Kyoto University Institute for Advanced Study (KUIAS), Kyoto University Yoshida Ushinomiya-cho, Sakyo-ku, Kyoto 606-8501, Japan.
b. Laboratory for Chemistry and Life Science, 4259 Tokyo Institute of Technology Nagatsuta, Midori-ku, Yokohama 226-8503, Japan.
c. JST-ERATO Yamamoto Atom Hybrid Project, Tokyo Institute of Technology, 4259 Nagatsuta Midori-ku, Yokohama 226-8503, Japan

that precisely modulates the alignment mode of dendritic ligands and facilitates the convergence to an anisotropic dendrimer. This heteroleptic system provided us with only single self-sorted products of bipolar-configured dendrimers in which steric repulsion among the dendritic ligands (macroligands) regulates the global self-assembly process to avoid the generation of isotropic byproducts (Fig. 1c). Cu^{II}-mediated co-assembly of carbazole dendritic macroligands ($\mathbf{IpG}n^{2-}$, n = 3–1, Fig. 2) and $\mathbf{L}^{2-}$ as the linker ligand were investigated; heteroleptic MOPs, $Cu_{12}\mathbf{IpG}n_6\mathbf{L}_6$, in which three dendrons are segregated at the top and bottom of each MOP core, were readily formed.[8] Of note, the highly crystalline nature of the carbazole dendrons enabled a single-crystal X-ray structure to be determined, from which the anisotropic bipolar arrangement of the MOP-core dendrimer was unambiguously identified.
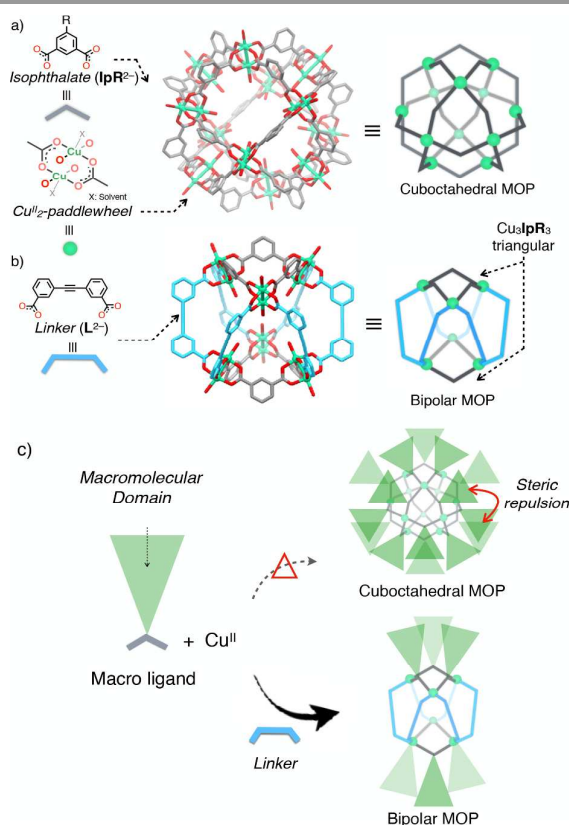

Fig. 1. Core structures of a) a homoleptic cuboctahedral MOP ($Cu_{24}\mathbf{IpR}_{24}$), and b) a heteroleptic bipolar MOP ($Cu_{12}\mathbf{IpR}_6\mathbf{L}_6$), where R represents a functional group at position-5 of the isophthalate. c) Illustrating the synthesis of a MOP-cored macromolecule using an organic ligand with a bulky dendritic macromolecular moiety in the absence (upper) and presence (bottom) of a linker ligand.

We designed the $H_2\mathbf{IpG3}$ macroligand, which is an isophthalic acid substituted with a third-generation (**G3**) carbazole dendron (Fig. 2). The macroligand was synthesized by the Ullman-type N–C coupling[8b] of a H-terminated carbazole dendron and dimethyl 5-iodoisophthalate, followed by alkaline hydrolysis (See ESI). The complexation between

Cu^{II} and $H_2\mathbf{IpG3}$ in the presence of $H_2\mathbf{L}$ was examined by monitoring the reaction mixture by size-exclusion chromatography (SEC) (Fig. 3).[6d,7] A new narrow peak was observed in the SEC trace at t = 16.8 min upon mixing equimolar amounts of $H_2\mathbf{IpG3}$ and $H_2\mathbf{L}$, and 2 equiv. of $Cu(OAc)_2 \cdot H_2O$ in N,N-diethylformamide (DEF) at room temperature, while the pristine $H_2\mathbf{IpG3}$ and $H_2\mathbf{L}$ organic ligands, were observed at t =18.6 and 19.9 min, respectively (Figs. 3b and S13–14, ESI). This indicates the formation of a discrete and stable supramolecular complex with a larger hydrodynamic volume than the pristine ligands under these conditions. The resulting complex was readily isolated as a pale-blue solid by precipitation from MeOH as a poor solvent (Fig. S14, ESI). The $\mathbf{IpG3}^{2-}:\mathbf{L}^{2-}$ ligand incorporation ratio in the product was determined to be 1:1 through integration of the ^{1}H NMR signals of the isolated sample digested in a 1:60 mixture of $DCl_{aq}:d_6$-DMSO (Fig. S11, ESI), which is in good agreement with that deduced from the aforementioned heteroleptic MOP architecture. Matrix-assisted laser-desorption-ionization–time-of-flight (MALDI-TOF) mass spectrometry of the resulting complex revealed a prominent peak at m/z = 10269.65, which is consistent with $[Cu_{12}\mathbf{IpG3}_6\mathbf{L}_6 – H]^-$ (Figs. 3c and S12).
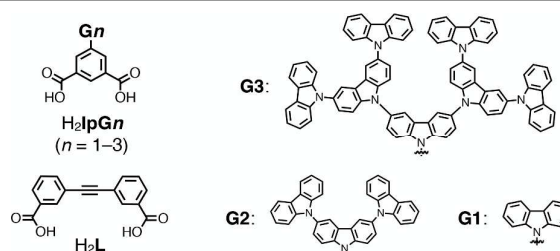

Fig. 2. Structures of isophthalic acids with third-to-first generation (**G3**-**G1**) carbazole dendrons ($H_2\mathbf{IpG}n$), and $H_2\mathbf{L}$ linker ligand, where n indicates the dendron generation.

Similar heteroleptic assemblies involving $H_2\mathbf{L}$ were also formed with the smaller macroligands (Fig. S13, ESI). We synthesized **G1**- and **G2**-substituted macroligands, namely $H_2\mathbf{IpG1}$ and $H_2\mathbf{IpG2}$, using analogous methods to that used to prepare $H_2\mathbf{IpG3}$. The corresponding heteroleptic MOPs, composed of the smaller macroligands, namely $Cu_{12}\mathbf{IpG1}_6\mathbf{L}_6$ and $Cu_{12}\mathbf{IpG2}_6\mathbf{L}_6$, were immediately formed in 1:1:2 mixtures of the corresponding isophthalic acid ($H_2\mathbf{IpG1}$ or $H_2\mathbf{IpG2}$), $H_2\mathbf{L}$, and $Cu(OAc)_2 \cdot H_2O$ in DEF at room temperature, as evidenced by the appearance of narrow SEC peaks at longer elution times in their SEC traces (t = 17.7 min for $Cu_{12}\mathbf{IpG1}_6\mathbf{L}_6$, t = 17.3 min for $Cu_{12}\mathbf{IpG2}_6\mathbf{L}_6$) than that of the previously discussed $Cu_{12}\mathbf{IpG3}_6\mathbf{L}_6$ (t = 16.8 min); this suggests the formation of discrete complexes with the smaller-generation dendrons than was observed for **G3**. Formation of each complex was also supported by mass spectrometry, which revealed prominent peaks corresponding to the respective heterotopic MOP architectures (See ESI).

Despite numerous attempts, no single crystal of $Cu_{12}\mathbf{IpG3}_6\mathbf{L}_6$ was obtained. Instead, we successfully obtained sufficient-quality single crystals of the smaller $Cu_{12}\mathbf{IpG2}_6\mathbf{L}_6$

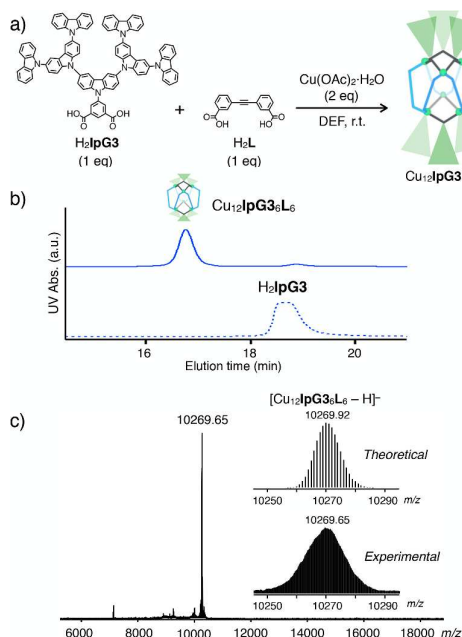analogue from a 1:1 (v/v) mixture of DEF and MeOH at room temperature.

Fig. 3. a) Synthesis of a heteroleptic bipolar MOP ($Cu_{12}IpG3_6L_6$). b) SEC traces of H_2IpG3 (dashed line) and a mixture (solid line) of H_2IpG3 (1 equiv.), H_2L (1 equiv.), and $Cu(OAc)_2·H_2O$ (2 equiv.) recorded at 313 K with a UV detector using THF as the eluent. c) MALDI-TOF mass spectra (negative-ion, *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile: DCTB matrix) of a mixture of H_2IpG3 (1 equiv.), H_2L (1 equiv.), and $Cu(OAc)_2·H_2O$ (2 equiv.) in THF.

Single-crystal X-ray diffraction (SXRD) analysis unambiguously revealed the molecular structure of $Cu_{12}IpG2_6L_6$ (Fig. 4a, S17–18, ESI); six $IpG2^{2-}$, six L^{2-}, and six Cu^{II}_2-paddlewheel clusters are linked together to form a heteroleptic bipolar polyhedral core. Three $IpG2^{2-}$ macroligands create two sets of Cu_3IpG2_3 triangular fragments through Cu^{II}-coordination, in which three dendrons are closely packed in the polar positions of the MOP core with dihedral angles of around 56–65° among the carbazole moieties (Fig. 4b). Each Cu_3IpG2_3 triangle is segregated by six L^{2-} units to afford an anisotropic structure with an aspect ratio of 1.7 (dimensions were calculated using the crystal structure to be 3.6 × 2.1 nm; length × width). Notably, the resulting single crystal was soluble in THF and exhibited a single narrow SEC peak at the identical elusion time to that of the aforementioned 2:1:1 mixture of $Cu(OAc)_2·H_2O$, H_2IpG2, and H_2L (Fig. S19, ESI), suggesting the formation of identical MOP structures in both solution and crystalline states. The molecular weights and aspect ratios of respective MOPs are summarized in Fig. 5d.

To further understand the formation behavior of these bipolar MOPs bearing carbazole dendrons, Cu^{II}-complexes of H_2IpG3 with different equivalents of the H_2L linker ligand ($x = [H_2L]_0/[H_2IpG3]_0 = 0$–1.5) were investigated; this study revealed the role of the H_2L unit in stabilizing the resulting anisotropic dendrimer. Mixtures of H_2IpG3 and x equivalents

of H_2L were reacted with equimolar amounts of $Cu(OAc)_2·H_2O$ relative to the sum of the organic ligands (i.e., $1 + x$ equiv.), and the amount of the resulting MOP ($Cu_{12}IpG3_6L_6$) was determined from the SEC peak area (Figs. 5a and c). The peak area ascribed to $Cu_{12}IpG3_6L_6$ increased in proportion to x, with increasing H_2L fraction, and converged when $x > 1$ (Fig. 5c). This result indicates that $IpG3^{2-}$ and L^{2-} undergo self-sorting through Cu^{II}-complexation to predominantly form the heteroleptic $Cu_{12}IpG3_6L_6$.[7,9]

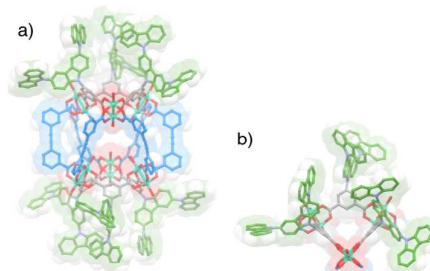**Fig. 4.** a) Crystal structure of $Cu_{12}IpG2_6L_6$. b) A partial structure of the triangular fragments of Cu_3IpG2_3 that are segregated at both polar positions of the polyhedral core. The peripheral carbazole moieties adopt two different disordering patterns: mode A and B, and the structure of disordering mode A is shown here (See Fig. S17 for mode B). Coordinating molecules at the axial positions of each Cu^{II}_2-paddlewheel cluster are represented by oxygen atoms. (C: gray, C of **L**: blue, C of **G2**: yellowish green, Cu: pale green, O: red, N: pale blue).
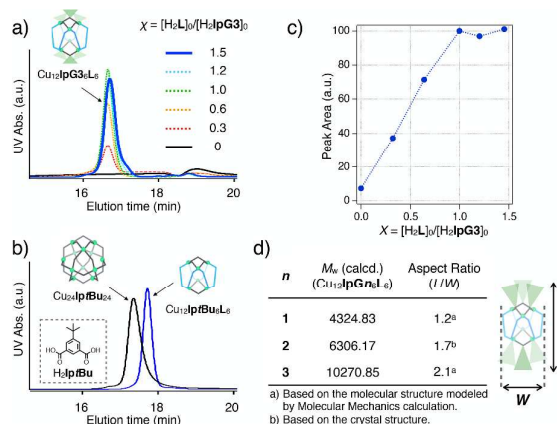

Fig. 5. SEC traces of a) mixtures of H_2IpG3 (1 equiv.) and different amounts (x equiv.) of H_2L in the presence of $1 + x$ equiv. of $Cu(OAc)_2·H_2O$ ($x = 0$–1.5) and b) a mixture of H_2IptBu and 1.0 equiv. (blue) or 0 equiv. (black) of H_2L in the presence of $Cu(OAc)_2·H_2O$ (equimolar to the total amount of ligand molecules present), recorded at 313 K with a UV detector using THF as the eluent. Inset shows the molecular structure of H_2IptBu. c) Plot of the SEC peak area assignable to $Cu_{12}IpG3_6L_6$ from Fig. 5a as a function of $x = [H_2L]_0/[H_2IpG3]_0$. Values are normalized against the $x = 1.0$ peak. d) Theoretical molecular weights and aspect ratios of MOPs.

As described above, some isophthalic acid derivatives (H_2IpR) have been reported to react alone with Cu^{II} to form homoleptic cuboctahedal $Cu_{24}IpR_{24}$ MOPs in the absence of H_2L (Fig. 1a).[5] Indeed, a 1:1 mixture of 5-*tert*-butylisophthalic acid (H_2IptBu, Fig. 5d) and $Cu(OAc)_2·H_2O$ in DEF initially forms $Cu_{24}IptBu_{24}$, which can clearly be detected as a distinct

monodispersed SEC peak at a shorter elution time (t = 17.3 min, black trace, Fig. 5b) than that of the bipolar heteroleptic $Cu_{12}IptBu_6L_6$ MOP (t = 17.7 min, blue trace, Fig. 5b) because of its larger hydrodynamic volume.[6d,7] In contrast, the above-mentioned Cu^{II}-complex with H_2IpG3 in the absence of H_2L (i.e., x = 0, black trace in Fig. 5a) exhibits no sharp SEC peak corresponding to the $Cu_{24}IpG3_{24}$ cuboctahedral MOP, which is expected to elute at a shorter time than $Cu_{12}IpG3_6L_6$. This observation suggests the homoleptic cuboctahedral $Cu_{24}IpG3_{24}$ MOP, the surface of which should be surrounded by **G3** dendrons, is not formed or is insufficiently stable to be clearly detected by SEC. A similarly broadened SEC trace was also observed for the 1:1 mixture of $Cu(OAc)_2 \cdot H_2O$ and isophthalate, and the lower-generation dendron, namely H_2IpG2 (Fig. S5, ESI). On the other hand, Cu^{II}-complexation with the smallest ligand (H_2IpG1) afforded the discrete $Cu_{24}IpG1_{24}$ complex, which was detected as a sharp SEC peak (t = 17.3 min, Fig. S5, ESI) and by the appearance of a prominent peak in the MALDI-TOF mass spectrum (m/z = 9427.20 for $[Cu_{24}IpG1_{24} - H]^-$, Fig. S6, ESI). Such consequences of dendritic effects in self-sorting has been also observed in the self-assembly of dendrimers with hydrogen-bonding motifs.[3a]

It is important to note that the molecular structure of the isotropic cuboctahedral MOP (i.e., $Cu_{24}IpR_{24}$, Fig. 1a) necessitates the congregation of a total of 24 isophthalates into a single cage structure with a diameter of only 2.4 nm. This, in turn, results in increased steric repulsion for the **G2** and **G3** macroligands that destabilized the isotropic cuboctahedral MOP structure, leading to the suppressed formation of the isotropic byproduct as a consequence, and/or its possible degradation during SEC analysis. This observation reminds us of the important roles that the linker ligands L^{2-} play; they prevent steric repulsion between the bulky dendrons while allocating macroligands in order to achieve anisotropic convergence, as evidenced by the crystal structure (Fig. 4). The electron-withdrawing properties of the carbazole dendrons might also affect the coordinating ability of isophthalate moiety, thereby further destabilizing the homoleptic cuboctahedral MOP.[8a]

In summary, we developed a facile synthetic approach to anisotropic dendrimers with well-defined bipolar arrangements of carbazole dendrons using a heteroleptic MOP as a core scaffold. SXRD analysis unambiguously revealed the bipolar structure of the product, in which bulky dendrons converge to each polar position of the heteroleptic MOP core. The linker ligands play crucial roles that modulate the ligand arrangement on the MOP core, thereby reducing steric repulsion among the bulky macroligands, and stabilizing the resulting anisotropic structure. The proposed approach, which employs a heteroleptic MOP as a core scaffold, provides a universal and facile route that promises high-precision macromolecular syntheses of complex anisotropic architectures.
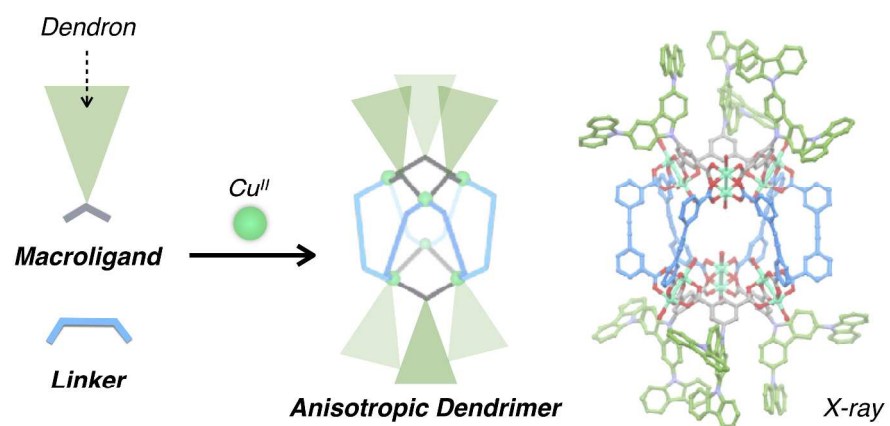
Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) W.-B. Zhang, X. Yu, C.-L. Wang, H.-J. Sun, I-F. Hsieh, Y. Li, X.-H. Dong, K. Yue, R. V. Horn and S. Z. D. Cheng, *Macromolecules*, 2014, **47**, 1221−1239; (b) G. Polymeropoulos, G. Zapsas, K. Ntetsikas, P. Bilalis, Y. Gnanou and N. Hadjichristidis, *Macromolecules*, 2017, **50**, 1253−1290.
2 (a) K. Ariga, H. Ito, J. P. Hill and H. Tsukube, *Chem. Soc. Rev.*, 2012, **41**, 5800−5835; (b) Y. Zhao, F. Sakai, L. Su, Y. Liu, K. Wei, G. Chen and M. Jiang, *Adv. Mater.*, 2013, **25**, 5215−5256; (c) Z. Liu, J. Qiao, Z. Niu, Q. Wang, *Chem. Soc. Rev.*, 2012, **41**, 6178−6194; (d) K. Matsuura, *RSC Adv.*, 2014, **4**, 2942−2953.
3 (a) Y. Ma, S. V. Kolotuchin, and S. C. Zimmerman, *J. Am. Chem. Soc.* 2002, **124**, 13757−13769; (b) S.-H. Hwang, C. D. Shreiner, C. N. Moorefieldc and G. R. Newkome, *New J. Chem.*, 2007, **31**, 1192−1217; (c) B. M. Rosen, C. J. Wilson, D. A. Wilson, M. Peterca, M. R. Imam and V. Percec, *Chem. Rev.*, 2009, **109**, 6275−6540; (d) D. Astruc, E. Boisselier. C. Ornelas, *Chem. Rev.*, 2010, **110**, 1857−1959; (e) M. Sowinska and Z. Urbanczyk-Lipkowska, *New J. Chem.*, 2014, **38**, 2168−2203; (f) X. Yan, B. Jiang, T. R. Cook, Y Zhang, J. Li, Y. Yu, F. Huang, H.-B. Yang, P. J. Stang, *J. Am. Chem. Soc.*, 2013, **135**, 16813−16816; (g) L. Xu, L.-J. Chen and H.-B. Yang, *Chem. Commun.*, 2014, **50**, 5156−5170; (h) S. Nakajima, K. Albrecht, S. Kushida, E. Nishibori, T. Kitao, T. Uemura, K. Yamamoto, U. H. F. Bunz, Y. Yamamoto, *Chem. Commun.*, 2018, **54**, 2534−2537.
4 (a) D. J. Tranchemontagne, Z. Ni, M. O'Keeffe and O. M. Yaghi, *Angew. Chem. Int. Ed.*, 2008, **47**, 5136−5147; (b) K. Harris, D. Fujita and M. Fujita, *Chem. Commun.*, 2013, **49**, 6703−6712; (c) N. Ahmad, A. H. Chughtai, H. A. Younus, and F. Verpoort, *Coord. Chem. Rev.*, 2014, **280**, 1−27.
5 (a) M. Eddaoudi, J. Kim, J. B. Wachter, H. K. Chae, M. O'keeffe and O. M. Yaghi, *J. Am. Chem. Soc.*, 2001, **123**, 4368−4369; (b) J.-R. Li and H.-C. Zhou, *Nat. Chem.*, 2010, **2**, 893−898.
6 (a) Y.-R. Zheng, K. Ghosh, H.-B. Yang and P. J. Stang, *Inorg. Chem.*, 2010, **49**, 4747−4749; (b) A. V. Zhukhovitskiy, M. Zhong, E. G. Keeler, V. K. Michaelis, J. E. P. Sun, M. J. A. Hore, D. J. Pochan, R. G. Griffin, A. P. Willard and J. A. Johnson, *Nat. Chem.*, 2015, **8**, 33−41; (c) S. Sato, M. Ikemi, T. Kikuchi, S. Matsumura, K. Shiba and M. Fujita, *J. Am. Chem. Soc.*, 2015, **137**, 12890−12896; (d) N. Hosono, M. Gochomori, R. Matsuda, H. Sato and S. Kitagawa, *J. Am. Chem. Soc.*, 2016, **138**, 6525−6531; (e) T.-Z. Xie, X. Wu, K. J. Endres, Z. Guo, X. Lu, J. Li, E. Manandhar, J. M. Ludlow, III, C. N. Moorefield, M. J. Saunders, C. Wesdemiotis and G. R. Newkome, *J. Am. Chem. Soc.*, 2017, **139**, 15652−15655.
7 N. Hosono, K. Omoto and S. Kitagawa, *Chem. Commun.*, 2017, **53**, 8180−8183.
8 (a) K. Albrecht and K. Yamamoto, *J. Am. Chem. Soc.*, 2009, **131**, 2245−2251; (b) K. Albrecht, K. Matsuoka, K. Fujita and K. Yamamoto, *Angew. Chem. Int. Ed.*, 2015, **54**, 5677−5682; (c) W.-J. Fan, B. Sun, J. Ma, X. Li, H. Tan, and L. Xu, *Chem. Eur. J.*, 2015, **21**, 12947−12959.
9 (a) M. M. Safont-Sempere, G. Fernández and F. Würthner, *Chem. Rev.*, 2011, **111**, 5784−5814; (b) Q.-F. Sun, S. Sato and M. Fujita, *Angew. Chem. Int. Ed.*, 2014, **53**, 13510−13513; (d) W. M. Bloch, and G. H. Clever, *Chem. Commun.*, 2017, **53**, 8506−8516.

Anisotropic dendrimers with bipolar shapes were systematically obtained using a heteroleptic metal-organic polyhedron (MOP) as a robust core scaffold.

310x155mm (300 x 300 DPI)